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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2001B–0431]

International Conference on Harmonisation; Final Recommendations on the Revision of the Permitted Daily Exposures for Two Solvents, N-Methylpyrrolidone and Tetrahydrofuran, According to the Maintenance Procedures for the Guidance Q3C Impurities: Residual Solvents; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing final recommendations to revise the permitted daily exposures (PDEs) for two solvents, n-methylpyrrolidone (NMP) and tetrahydrofuran (THF), according to the maintenance procedures for the guidance for industry entitled "Q3C Impurities: Residual Solvents." The final recommendations were reached under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

DATES: Submit written or electronic comments on guidance documents at any time.

ADDRESSES: Submit written comments on the analyses and recommendations to revise the PDEs for NMP and THF to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.* Submit written requests for single copies of the

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documents to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research , 1401 Rockville Pike, Rockville, MD 20852–1448, FAX 888–223–7329. Send two self-addressed adhesive labels to assist the office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to documents and maintenance procedures.

FOR FURTHER INFORMATION CONTACT:

Regarding the Q3C guidance: Robert Osterberg, Center for Drug Evaluation and Research (HFD–520), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2120; or Andrew Shrake, Center for Biologics Evaluation and Research (HFM–345), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1148, 301–402–4635.

Regarding the ICH: Michelle Limoli, Office of International Programs (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION:

I. Background

In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonisation of regulatory requirements. FDA has participated in many meetings designed to enhance harmonisation and is committed to seeking scientifically based, harmonized technical procedures for pharmaceutical development. One of the goals of harmonisation is to identify and then reduce

differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonisation initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonisation of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of December 24, 1997 (62 FR 67377), FDA published the ICH draft guidance for industry entitled "Q3C Impurities: Residual Solvents." The draft guidance makes recommendations as to what amounts of residual solvents are considered safe in pharmaceuticals. The draft guidance recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. Upon

issuance in 1997, the text and appendix 1 of the draft guidance contained several tables and a list of solvents categorizing residual solvents by toxicity, classes 1 through 3, with class 1 being the most toxic. The ICH Quality Expert Working Group (EWG) agreed that the PDE could be modified if reliable and more relevant toxicity data were brought to the attention of the group and the modified PDE could result in a revision of the tables and list.

In 1999, ICH instituted a Q3C maintenance agreement and formed a maintenance EWG (Q3C EWG). The agreement provided for the reconsideration of solvent PDEs and allowed for minor changes to the tables and list that include the existing PDEs. The agreement also provided that new solvents and PDEs could be added to the tables and list based on adequate toxicity data. In the **Federal Register** of February 12, 2002 (67 FR 6542), FDA briefly described the process for proposing future revisions to the PDEs. In the same notice, the agency announced its decision to delink the tables and list from the Q3C guidance and create a stand alone document entitled "Q3C: Tables and List" to facilitate making changes recommended by ICH.

In the **Federal Register** of February 12, 2002 (67 FR 6542), FDA also announced the availability of draft recommendations for the revision of the PDE for NMP and THF according to the Q3C maintenance procedures. The notice gave interested persons an opportunity to submit comments by March 14, 2002.

II. Revised PDEs for NMP and THF

After consideration of the comments received, the EWG's recommendations to revise the PDEs for NMP and THF were submitted to the ICH Steering Committee and agreement was reached by the three participating regulatory agencies in September 2002.

A. N-Methylpyrrolidone (NMP)

The Q3C EWG received new toxicity data for the solvent NMP in late 1999. In February 2002, FDA made available for comment the EWG's draft recommendation for the revision of the PDE for NMP (67 FR 6542 at 6543). At the September 2002 ICH meeting, the Steering Committee agreed to the EWG's recommendation to keep NMP in Class 2. A PDE of 5.3 milligrams per day (mg/day) and a concentration limit of 530 parts per million (ppm) are being declared for this solvent.

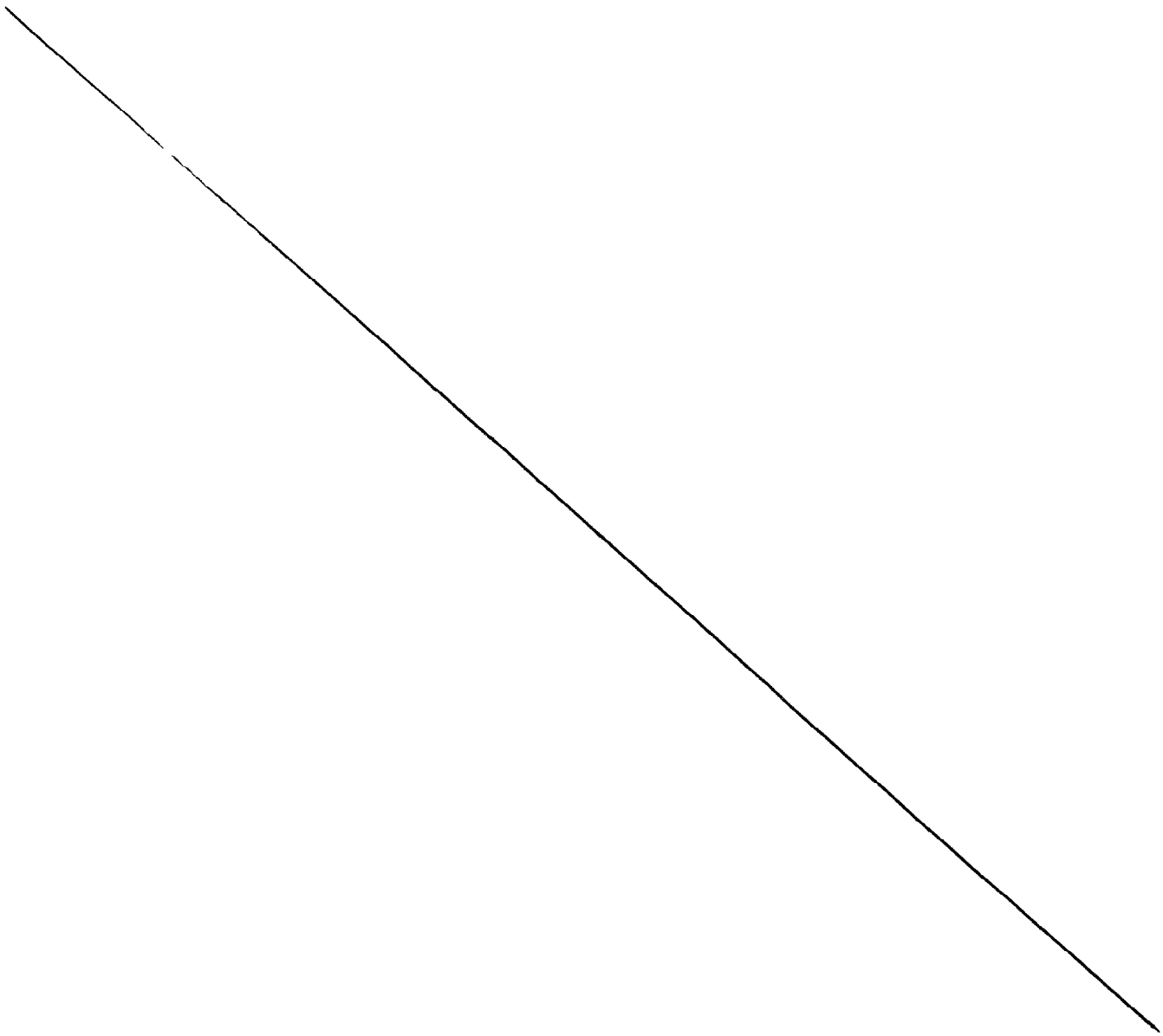
B. Tetrahydrofuran (THF)

The Q3C EWG reviewed new toxicity data for the solvent THF. In February 2002, FDA made available for comment the EWG's draft recommendation for the revision of the PDE for THF (67 FR 6542 at 6543). At the September 2002 ICH meeting, the Steering Committee agreed to the EWG's recommendation to move THF from class 3 to class 2. A PDE of 7.2 mg/day and a concentration limit of 720 ppm are being declared for this solvent.

The analyses and recommendations for NMP and THF are available for review at *http://www.fda.gov/cder/audiences/iact/iachome.htm*. They are also available from the Division of Drug Information (HFD–240) (see **ADDRESSES**). The agency will revise the tables and list in the guidance "Q3C: Tables and List" to reflect the ICH final recommendations for NMP and THF.

The revised PDEs for the two solvents contained in the revised guidance "Q3C: Tables and List" represent the agency's current thinking on this topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the list and on guidance documents at any time. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The analyses and recommendations and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.



III. Internet Access to Documents and the Maintenance Procedures

Persons with access to the Internet may obtain the Q3C documents at *http://www.fda.gov/cder/guidance/index.htm*, or *http://www.fda.gov/cber/guidelines.htm*. Information on the Q3C maintenance process, and proposals, recommendations, and agreements for revisions to the tables and list are made available at *http://www.fda.gov/cder/audiences/iact/iachome.htm*. The electronic address for the Division of Dockets Management is *http://www.fda.gov/ohrms/dockets/default.htm*.

Dated: 11/4/03

November 4, 2003.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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